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Regression of left ventricular mass in athletes undergoing complete detraining is mediated by decrease in intracellular but not extracellular compartments

Swoboda, Regression of myocardial mass on detraining

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Abstract

Background

Athletic cardiac remodelling can occasionally be difficult to differentiate from pathological hypertrophy. Detraining is a commonly used diagnostic test to identify physiological hypertrophy which can be diagnosed if hypertrophy regresses. We aimed to establish if athletic cardiac remodelling assessed by cardiovascular magnetic resonance (CMR) is mediated by changes in intracellular or extracellular compartments, and whether this occurs by one or three months of detraining.

Methods

Twenty-eight athletes about to embark on a period of forced detraining due to incidental limb bone fracture underwent clinical assessment, electrocardiogram and contrast enhanced CMR within a week of their injury, and then one month and three months later.

Results

After one month of detraining there was reduction in left ventricle (LV) mass (130 ± 28 g to 121 ± 25 g, $P<0.0001$), increase in native T1 (1225 ± 30 ms to 1239 ± 30 ms, $P=0.02$) and extracellular volume fraction (ECV, $24.5\pm 2.3\%$ to $26.0\pm 2.6\%$, $P=0.0007$) with no further changes by three months. The decrease in LV mass was mediated by a decrease in intracellular compartment volume (94 ± 22 ml to 85 ± 19 ml, $P<0.0001$) with no significant change in the extracellular compartment volume.

High LV mass index, low native T1 and low ECV at baseline were all predictive of regression in LV mass in the first month.

Conclusions

Regression of athletic LV hypertrophy can be detected after just one month of complete detraining and is mediated by a decrease in the intracellular myocardial compartment with no change in the extracellular compartment. Further studies are needed in athletes with overt and pathological hypertrophy to establish if native T1 and ECV may complement electrocardiography, echocardiography, cardiopulmonary exercise testing and genetic testing in predicting the outcome of detraining.

Key words

Cardiovascular magnetic resonance, athlete's heart, T1 mapping, extracellular volume fraction

Non-standard Abbreviations and Acronyms

AUC	Area under curve
CMR	Cardiovascular magnetic resonance
ECV	Extracellular volume fraction
HCM	Hypertrophic cardiomyopathy
LGE	Late gadolinium enhancement
MOLLI	Modified Look Locker inversion recovery
ROC	Receiver operator characteristic
TE	Echo time
TR	Repetition time

1 **Commentary**

2 Regular athletic training leads to physiological cardiac adaptation, namely biventricular
3 dilatation and left ventricle hypertrophy, sometimes termed “athlete’s heart”. Cross-sectional
4 studies using cardiovascular magnetic resonance T1 mapping imply that athletic left ventricle
5 hypertrophy is mediated by an increase in the intracellular compartment (predominantly
6 myocytes), with a relatively constant extracellular compartment (extracellular matrix and
7 capillary vasculature).

8 We studied athletes who were about to embark on a period of forced detraining due to incidental
9 limb bone fracture within a week of their injury, and then one month and three months later.
10 On complete detraining athletic left ventricle hypertrophy regressed within a month, which was
11 mediated by decrease in the size of the cellular compartment with no change in the extracellular
12 compartment.

13 T1 mapping is a powerful tool to investigate mechanisms and reversibility of hypertrophy in
14 athletes and may have a role in predicting the outcome of detraining. However, it remains to
15 be validated in athletes with abnormal ECG and suspected cardiomyopathy.

1 **Introduction**

2 The regular training that is required to participate in competitive sport leads to physiological
3 cardiac adaptation, namely biventricular dilatation and left ventricle (LV) hypertrophy,
4 sometimes termed “athlete’s heart”.¹ LV hypertrophy that overlaps into the pathological range
5 is relatively rare although does occur more commonly in participants of certain sports such as
6 rowing and cycling, and in male and black athletes.²

7 Cardiovascular magnetic resonance (CMR) is commonly used in the assessment of athletes
8 with LV hypertrophy as it allows both visualisation of the LV in multiple imaging planes and
9 detection of focal scar by late gadolinium enhancement imaging (LGE). T1 mapping by CMR
10 has been proposed to investigate cardiac tissue characteristics in athletes. Athletes have lower
11 cardiac extracellular volume fraction (ECV) than sedentary controls and the fittest athletes have
12 the lowest ECV.^{3,4} These cross-sectional findings imply that athletic LV hypertrophy is
13 mediated by an increase in the intracellular compartment (predominantly myocytes), with a
14 relatively constant extracellular compartment (extracellular matrix and capillary vasculature).
15 Conversely, areas of hypertrophy in hypertrophic cardiomyopathy have increased ECV and
16 initial data suggests that this divergent pattern might be useful to differentiate it from athlete’s
17 heart.⁵

18 Neither native T1 or ECV has been validated histologically in athletic hypertrophy. However
19 preclinical models of athlete’s heart have shown that increase in LV mass in exercise trained
20 rats is not associated with increase in collagen fraction, therefore implying it is mediated by
21 increase in myocyte mass.^{6,7}

22 Detraining is a commonly used test to diagnose athletic remodelling, although data supporting
23 its use are limited. After long term cessation of training regression of hypertrophy and dilatation
24 occurs in 80% of athletes with cardiac dimensions outside the normal range.⁸ A minimum of

1 three months detraining is typically required to demonstrate regression of LV hypertrophy
2 albeit with reduction in training rather than complete cessation.^{9,10} Compliance with detraining
3 is often poor and it is unpopular with athletes of all level. There is therefore a need to improve
4 the identification of athlete's heart by non-invasive imaging and predict the outcome of
5 detraining.

6 We hypothesised that in athletes who completely stop all forms of training, regression of LV
7 hypertrophy occurs in one month and is mediated by a decrease in intracellular compartment
8 volume. We aimed to investigate whether T1 mapping findings at baseline are predictive of the
9 cardiac consequences of detraining.

10 **Methods**

11 The data that support the findings of this study are available from the corresponding author
12 upon reasonable request. We prospectively recruited athletes presenting to the emergency
13 department in Leeds Teaching Hospitals NHS Trust with a limb bone fracture for which they
14 were advised to stop training for a minimum of six weeks. Only athletes age 18-45 were
15 included and had to be training for >4 hours a week for >2 years to participate. Exclusion
16 criteria were any significant past medical history, any regular medication or self-reported use
17 of anabolic steroids. Some athletes were able to recommence light training (fewer hours and
18 lower intensity than pre-injury levels) prior to their three month appointment and this was not
19 prohibited by the research team. The study was approved by the National Research Ethics
20 Service (16/EM/0399) and all participants gave written informed consent.

21 Appointments occurred within a week of the injury, one month and three months later. At each
22 appointment athletes underwent clinical assessment, contrast enhanced CMR and 12 lead
23 electrocardiogram (ECG). 12 lead ECG (MAC500, GE Medical Systems, Milwaukee, WI,
24 USA) was analysed by 2 physicians blinded to clinical details according to international

1 guidelines for ECG interpretation in athletes.¹¹ LV mass was estimated from ECG by the
2 Sokolow-Lyon product, the voltage sum of the greatest S wave in V1/2 and R wave in V5/6.¹²
3 A full blood count, for measurement of haematocrit, was taken at the time of intravenous
4 cannulation prior to each CMR study.

5 **Cardiovascular Magnetic Resonance Acquisition**

6 Participants underwent CMR on a dedicated cardiovascular 3 Tesla Philips Achieva system
7 equipped with a 32 channel coil and MultiTransmit® technology. Data were acquired during
8 breath-holding at end expiration. Balanced steady state free precession (SSFP) cine images
9 covering the entire heart in the LV short axis were acquired prior to contrast administration
10 (repetition time (TR) 2.7ms, echo time (TE) 1.3ms, matrix 320 x 320, slice thickness 10mm
11 with no gap, 30 cardiac phases).

12 T1 maps were acquired in a three short axis slices. Native T1 mapping used a breath-held
13 Modified Look-Locker Inversion recovery (MOLLI) acquisition (ECG triggered 5s(3s)3s,
14 single-shot, SENSE factor 2, prepulse delay 350ms, trigger delay set for end-diastole
15 (adaptive), flip angle 20°, matrix 400 x 400, slice thickness 10mm, giving a reconstructed voxel
16 size of 1.17 x 1.17mm).

17 0.15 mmol/kg of gadobutrol was administered through an intravenous cannula with a 10ml
18 saline flush (Gadovist®, Bayer Pharma, Berlin, Germany).

19 Tissue tagging by spatial modulation of magnetization (SPAMM) (spatial resolution
20 $1.51 \times 1.57 \times 10 \text{ mm}^3$, tag separation 7 mm, ≥ 18 phases, TR 5.8ms, TE 3.5ms, flip angle 10°,
21 typical temporal resolution 55 ms) was acquired in the three short axis slices.¹³

1 Late gadolinium enhancement (LGE) in matching LV short axis planes were carried out more
2 than 6 minutes after contrast administration. Typical parameters were TR 3.7ms, TE 2.0ms,
3 flip angle 25°, matrix 512 x 512, slice thickness 8mm with 2mm gap.

4 Post contrast T1 mapping was carried out exactly 15 minutes following last contrast injection
5 using 4s(3s)3s(3s)2s MOLLI acquisition with identical positioning and planning to the native
6 T1 map.

7 **Cardiovascular Magnetic Resonance Analysis**

8 CMR data were assessed quantitatively using commercially available software blinded to
9 detraining status (CVI42, Circle Cardiovascular Imaging Inc. Calgary, Canada). Epicardial and
10 endocardial borders were traced offline on the short axis cine stack at end-diastole and end-
11 systole to calculate LV and right ventricle (RV) end-diastolic volume (EDV), end- systolic
12 volume (ESV), stroke volume (SV), ejection fraction (EF) and LV mass. Papillary muscles
13 were excluded from all measurements. Indexed cardiac parameters were divided by body
14 surface area calculated by the Mosteller equation at baseline. ¹⁴ LGE imaging was analysed
15 visually to assess for the presence of scarring.

16 Pre and post contrast myocardial T1 values with a 3-parameter exponential fit with Look-
17 Locker correction were measured from short axis slices in the septum. Average measurements
18 from the basal and mid ventricular slices were used. Data from the apical slice was not used
19 because it was vulnerable to partial volume effects due to decreased wall thickness. ECV was
20 calculated from native and post contrast T1 times of myocardium and blood pool and
21 haematocrit as previously reported. ¹⁵

22 Intracellular compartment volume was calculated by multiplying (1-ECV) x (LV mass/1.05).

23 Extracellular compartment volume was calculated by multiplying ECV x (LV mass/1.05). ¹⁶

1 Tagging analysis was conducted using inTag (v1.0 CREATIS lab, Lyon, France). Endocardial
2 and epicardial contours were drawn on the short axis SPAMM sequences using a semi-
3 automated process as reported previously.¹³ Peak LV circumferential strain was measured for
4 the three slices.

5 **Statistical analysis and power calculation**

6 Statistical analysis was performed using IBM SPSS® Statistics 22.0 (IBM Corp., Armonk,
7 NY). Continuous variables were expressed as mean \pm SD or median (interquartile range)
8 depending upon normality. Categorical variables were expressed as N (%). Paired data at
9 baseline one and one month were compared by paired t test. When comparing three paired
10 groups, analysis of variance (ANOVA) with repeated measures was used. $P < 0.05$ was
11 considered statistically significant.

12 Receiver operating characteristic analysis was used to determine the diagnostic accuracy
13 baseline imaging parameters to predict regression of left ventricular hypertrophy ($>10g$) or
14 cavity dilatation ($>10ml$). The diagnostic accuracy is expressed as area under the curve (AUC)
15 and 95% confidence interval. Optimal sensitivity and specificity were calculated using Youden
16 index. Variables were combined by binary logistic regression. AUCs were compared by using
17 validated methods described by DeLong et al¹⁷.

18 The study was powered to detect a 7.5% decrease in indexed intracellular compartment volume
19 after one month of detraining. Assuming that baseline indexed intracellular compartment
20 volume would be comparable to low performance athletes in our previous study, which was
21 $47 \pm 6 ml/m^2$ a minimum sample size of 25 athletes would be required (power=0.8, $\alpha=0.05$).³

1 **Results**

2 Thirty-five athletes agreed to take part in the study between November 2016 and March 2018.
3 One athlete was unable to complete the study because of claustrophobia, one withdrew because
4 of possible pregnancy and five withdrew consent after the first scan but before the second scan.
5 The final cohort of 28, included 23 male and 5 female athletes with a median age of 24 (IQR:
6 21 - 30) years. Twenty-three athletes completed the whole protocol, with five athletes
7 withdrawing after their one month scan because they had resumed full training. Baseline
8 characteristics and their progression throughout the study are shown in **Table 1**. There were 31
9 ± 5 days between the baseline and one month scan, and 94 ± 10 days between the baseline and
10 three month scans. Athletes trained in a wide range of sports including soccer 9, rugby 5,
11 running 4, mixed sports 4, cycling 3, hockey 1, netball 1 and triathlon 1. Prior to their injury
12 athletes trained median 7 hours per week (IQR 5-9).

13 **Changes in Surface Electrocardiogram**

14 On one month detraining there was a significant decrease in the voltage of the R wave in chest
15 lead V₅ and the Sokolow-Lyon product, both electrical markers of left ventricular mass, **Table**
16 **2**. There were no significant changes in heart rate, PR interval or QTc.

17 **Changes in Ventricular Morphology**

18 After one month of complete detraining there was a 9.3g (7%, $P < 0.0001$) reduction in LV mass
19 with no further reduction between one and three months, **Figure 1 and Table 3**. This remained
20 significant when indexed to baseline body surface area. In the first month there were significant
21 increases in native T1 and ECV, **Figure 2**. There was a decrease in intracellular compartment
22 volume (8.4ml, 9%, $P < 0.0001$) with no significant change in the extracellular compartment
23 mass, **Figure 3**.

1 After one month of complete detraining there were significant comparable decreases in the end
2 diastolic volumes of both ventricles (Δ LV -8.2ml, -4.3%, $P=0.003$; Δ RV -7.8ml, -4.1%,
3 $P=0.03$). By three months of detraining there was no further decrease in end diastolic volume
4 of either ventricle, **Table 3**. There was no difference in these temporal changes when they were
5 indexed to baseline body surface area. There was no significant change in LV EF throughout
6 detraining, but there was a reduction in RV EF after one month due to decreased RV EDV.

7 No athlete had scarring detected on LGE imaging on any scan.

8 After one month of detraining there were non-significant absolute increases in peak
9 circumferential strain all three levels (Δ apex 0.4%, $P=0.61$; Δ mid LV 1.1%, $P=0.30$; Δ base
10 1.4% $P=0.06$). There were no further changes at three months.

11 **Comparison of those who had and who had not resumed training.**

12 Between the one month and three month scan 11/23 athletes were able to restart light training,
13 but were still not able to resume full training. When athletes were split according to those who
14 had resumed light training ($N=11$) and those who had not ($N=12$) there was no difference in
15 any LV or RV volumetric parameter, native T1 or ECV, **Supplementary Table 1**.

16 **Baseline parameters to predict cardiac regression**

17 High LV mass index, low native T1 and low ECV at baseline were all predictive of an absolute
18 LV mass regression in one month of detraining of more than 10g ($P=0.0006$, 0.04 and 0.03
19 respectively) **Supplementary Table 2**. The difference in diagnostic accuracy between LV
20 mass index and native T1 ($P=0.58$) or ECV ($P=0.71$) was not significant. When LV mass index
21 was combined with either native T1 or ECV by a binary logistic model there was an
22 improvement in diagnostic accuracy, **Supplementary Table 2**. None of LV EDV index, native
23 T1 or ECV were predictive of absolute LV EDV regression in one month of detraining of more

1 than 10ml. Only RV EDV index, but not native T1 or ECV, were predictive of absolute RV
2 EDV regression in one month of detraining of more than 10ml.

3 **Discussion**

4 We have shown that in athletes after just one month of complete detraining there is regression
5 of LV mass, LV EDV and RV EDV. There was no further regression of any measure by three
6 months of detraining. The regression of LV mass is mediated by a decrease in intracellular
7 compartment volume (predominantly cardiac myocytes) with no change in extracellular
8 compartment volume. High baseline LV mass is the strongest predictor of regression of LV
9 hypertrophy after one month of detraining. Low native T1/ECV were also predictive of LV
10 mass regression at one month and may have a role in the diagnosis of athlete's heart.

11 **Insights into the mechanisms of athletic ventricular remodelling**

12 We have demonstrated that regression in LV mass is mediated by a decrease in the intracellular
13 myocardial compartment with no change in the size of extracellular compartment. Previous
14 studies have demonstrated that athletes have lower ECV than sedentary controls and that the
15 fittest athletes have the lowest ECV.^{3,4} These studies were cross-sectional and therefore cannot
16 be used to attribute causality. Our present study is the first to show a longitudinal relationship
17 between LV mass, ECV and training, confirming the hypothesis that athletic hypertrophy is
18 mediated by an increase in the cellular compartment.

19 When T1 mapping data and LV mass are combined it is possible to dichotomise the
20 myocardium into cellular and extracellular compartments. This pattern is particularly relevant
21 in hypertrophic phenotypes and has been validated most comprehensively in aortic stenosis
22 where the derived extracellular compartment volume has a strong correlation with diffuse
23 fibrosis on biopsy¹⁸ and there is regression of both the cellular and extracellular compartments
24 after aortic valve replacement.¹⁶

1 The most important differential diagnosis in the young athlete with LV hypertrophy is
2 hypertrophic cardiomyopathy. CMR tissue characterisation has been histologically validated
3 in hypertrophic cardiomyopathy and can be used to detect both diffuse fibrosis (increased ECV)
4 and replacement fibrosis (focal LGE).^{19, 20} High level athletes with hypertrophic
5 cardiomyopathy are reported to have an altered phenotype with more prominent cavity
6 dilatation but replacement fibrosis is still identified in 33%.²¹ In hypertrophic cardiomyopathy
7 focal fibrosis is progressive and the extent of LGE increases progressively over the course of
8 the disease.²² Saberi et al performed a study of 113 patients with hypertrophic cardiomyopathy
9 who were randomised to a 16 week programme of moderate intensity exercise or standard care.
10²³ They reported that exercise training led to increased exercise capacity, but did not change
11 ventricular volumes or the extent of focal fibrosis on LGE.

12 It would be appealing to conduct a study of detraining in high level athletes with HCM to
13 investigate reversibility of changes in cellular and extracellular compartments. However, in
14 practice such a study would be almost impossible given the small number of patients with
15 hypertrophic cardiomyopathy who participate in competitive sport and their low willingness to
16 voluntarily detrain.

17 T1 mapping in athlete's heart has not been validated histologically. However there are
18 preclinical rat models of exercise induced cardiac hypertrophy, which suggest physiological
19 hypertrophy is not mediated by increase in myocardial collagen.^{6,7} Benito et al trained rats to
20 run on a treadmill for an hour a day.²⁴ After 8 weeks of training there was an 11% increase in
21 LV mass, but no alteration in the hydroxyproline (a modified amino-acid found specifically in
22 collagen) content of the whole left ventricle. These results are in keeping with our finding that
23 athletic hypertrophy is mediated by preferential expansion of the intracellular compartment.

1 **Effects of detraining on cardiac morphology**

2 Previous studies have demonstrated that the heart is highly adaptable to physical training and
3 cross sectional studies have clearly demonstrated a dose response relationship between degree
4 of fitness (measured quantitatively by cardiopulmonary exercise test) and extent of LV and RV
5 remodelling.²⁵ Arbab-Zadeh et al demonstrated in a longitudinal study of 12 previously
6 sedentary subjects when trained for endurance sport development of cardiac athletic
7 remodelling, albeit to a lesser extent than that seen in elite athletes.²⁶ They reported that in the
8 first three months of training there were significant increases in RV EDV and LV mass with
9 increase in LV EDV by 6 months. Most of the subjects were training for the marathon and it is
10 not known whether these longitudinal patterns of remodelling apply to other sports or training
11 regimes. Cardiac hypertrophy regression with detraining in our study was quicker, taking only
12 one month, compared to remodelling on commencement of training which took at least 3
13 months in the previous study.²⁶ Although it should be noted the previous study did not conduct
14 imaging at one month and participants in both studies conducted different sports with different
15 baseline fitness.

16 The evidence of regression of athletic ventricular remodelling with detraining largely predates
17 CMR and studies were conducted by echocardiography. Maron et al reported that LV mass
18 measured by echocardiography in 6 Olympic rowers/canoeists decreased by 75g (24%) in a
19 voluntary period (mean 13 weeks) of detraining following the 1988 Seoul Olympic Games.⁹
20 Weiner et al reported a significant regression in LV mass of 4 college American Football
21 players with LV hypertrophy after 3 months of voluntary detraining that returned to pre-
22 training level by 6 months.¹⁰ In a cohort of 40 Olympians Pellicia et al reported a 28%
23 reduction in LV mass after long term detraining (1-13 years).⁸ These studies included athletes
24 with LV hypertrophy at baseline (>12mm interventricular septum) and included athletes at the
25 pinnacle of fitness. The LV hypertrophy was more pronounced in these studies than ours,

1 reflecting the fitness of the athletes studied. The extent of LV mass regression was therefore
2 greater (24-28% vs 7%). These studies defined detraining as reduction in exercise intensity
3 rather than complete cessation perhaps explaining why regression of LV mass not reported
4 until three months compared to one month in our study.

5 Pedlar et al performed echocardiography in 21 amateur runners after an 18 week training
6 programme and then after 4 and 8 weeks when participants were limited to <2 hours of training
7 a week.²⁷ Similarly to our findings they reported a 10.4% reduction in LV mass after 4 weeks
8 with no change in LV EDV even 8 weeks post-race.

9 The finding of early regression of LV mass is not unique to athletes, and has been reported in
10 by CMR in healthy individuals (N=5) after 6 weeks complete voluntary bed rest²⁸ and by
11 echocardiography in astronauts (N=38) immediately after a 9-16 day spaceflight.²⁹

12 The mean LV mass in the present study (130 ± 28 g) was comparable to low performance male
13 athletes in our previous study (129 ± 17 g) who had a mean VO_{2max} of 60 ± 8 mls/kg/min. If we
14 had been able to recruit higher performance athletes with higher LV mass at baseline we may
15 have been able to detect a further decrease in LV mass between one and three months. An
16 alternative explanation is that the pattern of regression reflects the nature of detraining. Athletes
17 were most incapacitated immediately after their fracture leading to most regression in this
18 period. Throughout the subsequent recovery the levels of physical activity gradually increased
19 affecting the regression response.

20 Using the same CMR tagging methodology we have previously shown that athletes have lower
21 peak circumferential strain than sedentary controls.¹³ In the current study, we found that in all
22 three levels there was a no significant increase in strain on detraining, despite significant
23 decreases in LV mass and intracellular compartment in the same period.

1 **Limitations**

2 In this study we relied upon self-reported abstinence from training and it is therefore possible
3 that athletes carried out training that was not reported to the research team. We have not
4 conducted an objective assessment of fitness using cardiopulmonary exercise test but this was
5 not possible due to the nature of the participants' injuries. Athletes in this study participated in
6 a range of sports which giving different patterns of athletic remodelling at baseline. We did not
7 collect data on non-steroidal anti-inflammatory use which may have caused fluid retention and
8 altered the myocardial extracellular compartment. We have not studied athletes with an
9 abnormal ECG, overt LV hypertrophy (12-15mm) or cardiomyopathy and patterns of
10 regression in these groups remains to be established.

11 T1 mapping has only been validated histologically in disease and is difficult to validate in
12 athlete's heart. Native T1 (and less so ECV) vary by field strength, manufacturer and pulse
13 sequence. At present it is recommended that normal values specific to the scanner and
14 acquisition protocol are used to determine ECV in the athlete with unexplained LV hypertrophy
15 ³⁰.

16 **Conclusions**

17 Regression of athletic LV hypertrophy can be detected after just one month of complete
18 detraining and is mediated by a decrease in the intracellular myocardial compartment with no
19 change in the extracellular compartment. Further studies are needed in athletes with overt and
20 pathological hypertrophy to establish if native T1 and ECV may complement
21 electrocardiography, echocardiography, cardiopulmonary exercise testing and genetic testing
22 in predicting the outcome of detraining.

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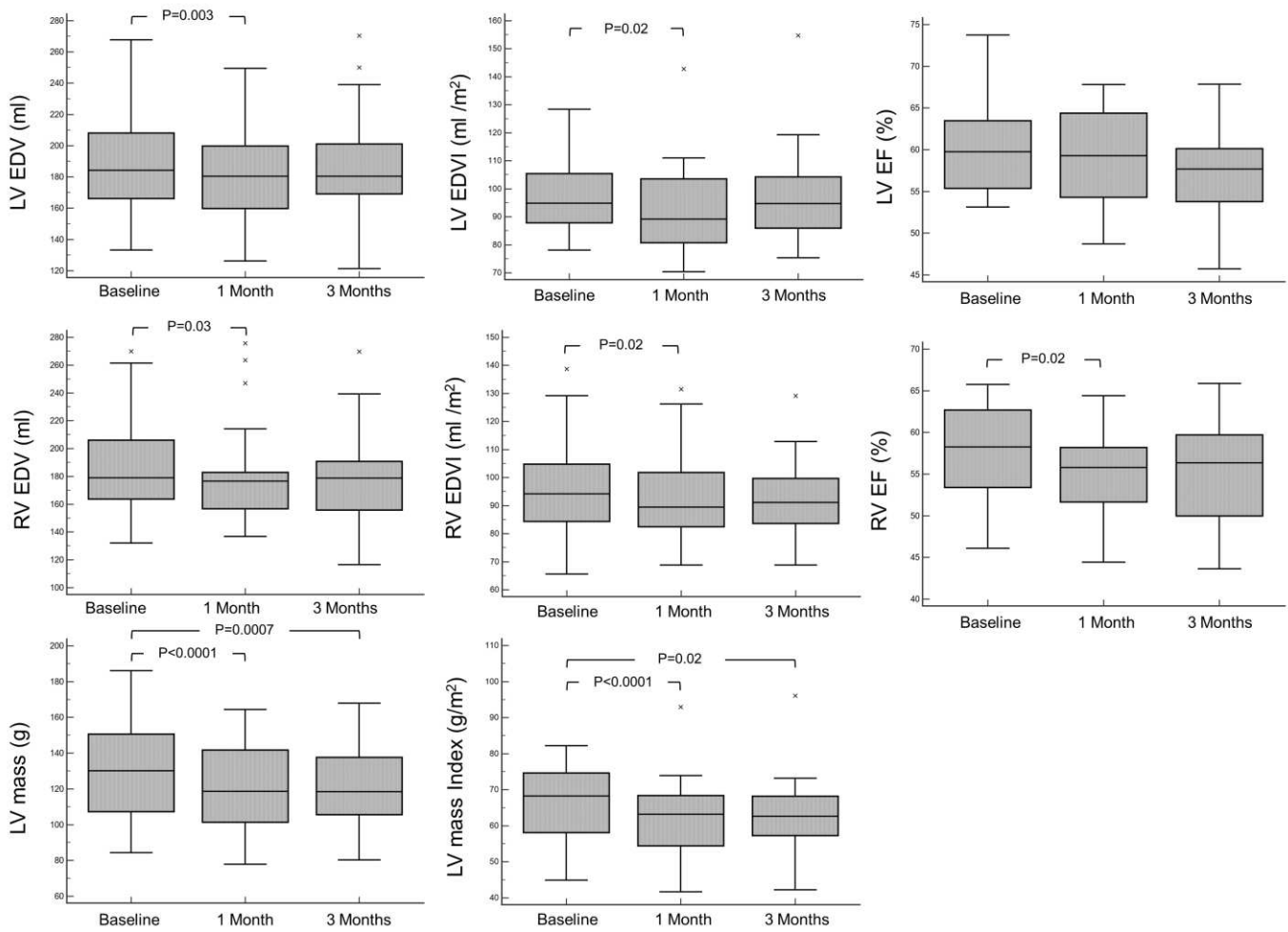


Figure 1. Change in cardiac morphology on detraining. Change in left and right ventricular end diastolic volume (EDV), ejection fraction (EF) and mass after one and three months detraining.

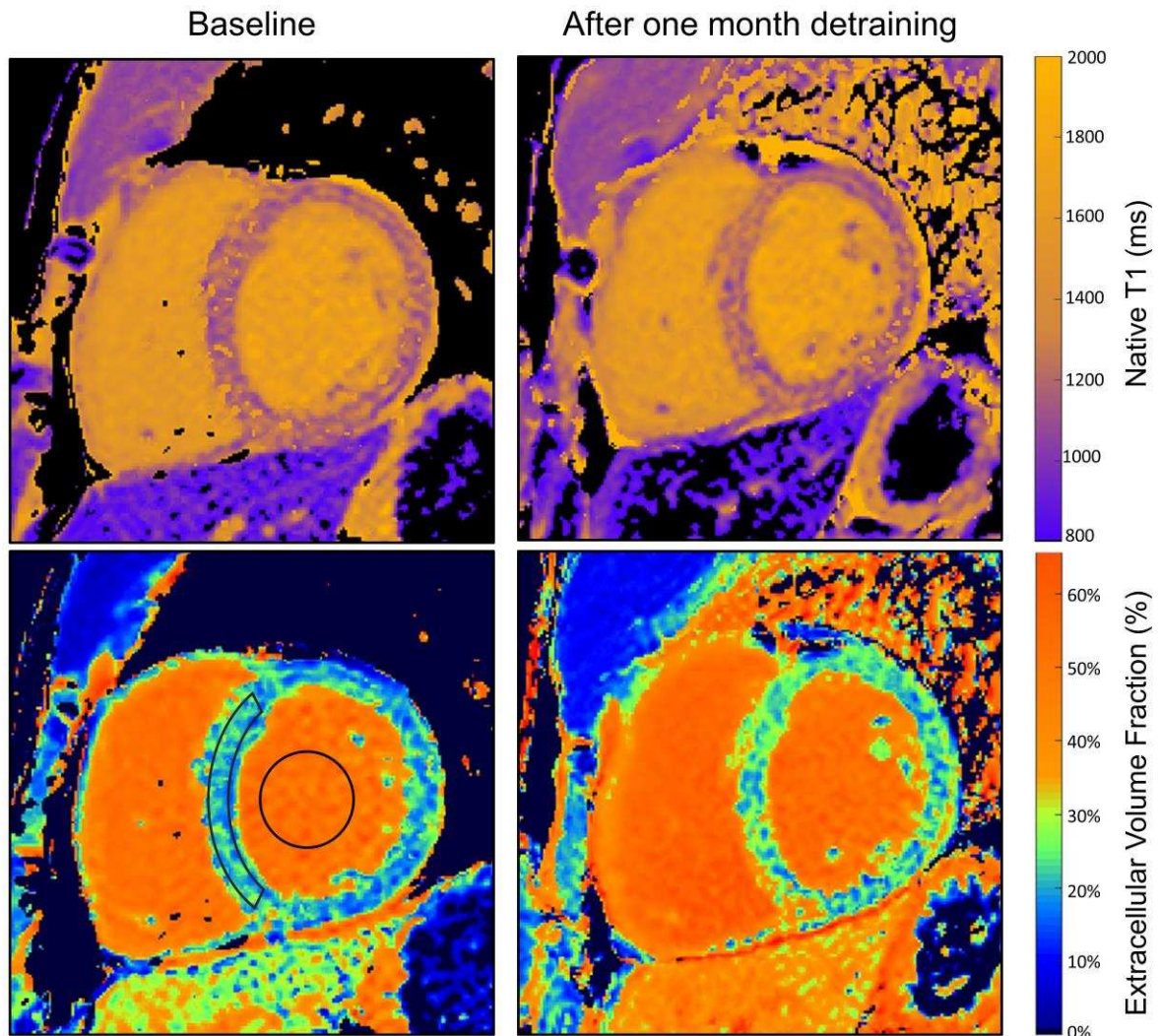


Figure 2. Native T1 and ECV (extracellular volume fraction) maps before and after one month of detraining. Native T1 (above) and ECV (below) maps from a rugby player before and after one month of detraining. Over this period native T1 increased from 1160ms to 1213ms, ECV increased from 19.5% to 23.3% and LV mass decreased from 186g to 164g. Typical myocardial and blood pool contours are shown in the lower left panel.

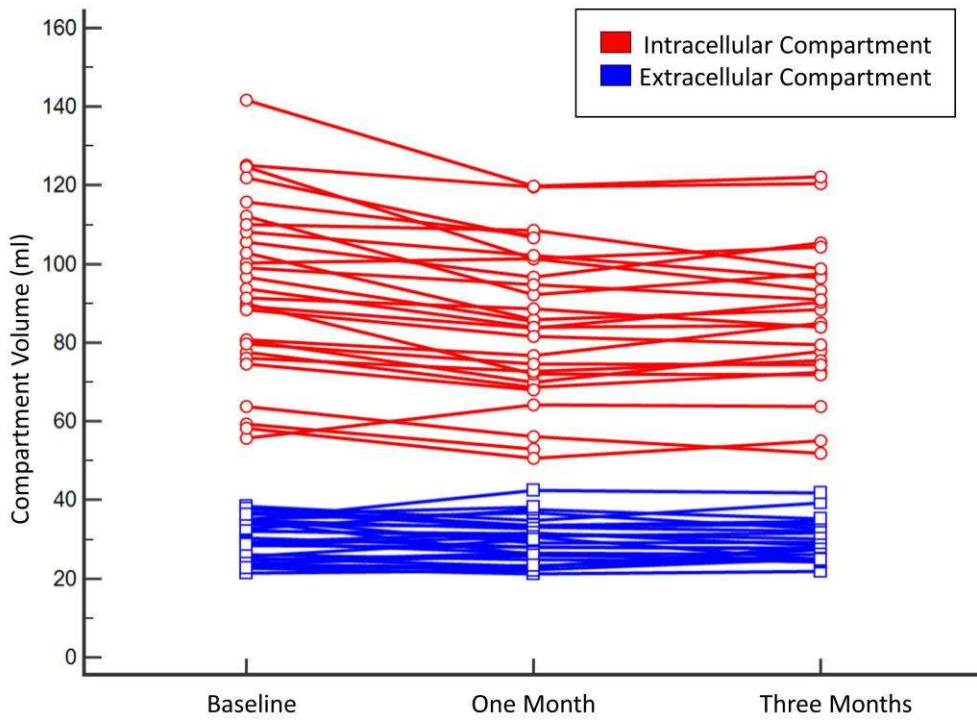


Figure 3. Change in cardiac compartment volumes on complete detraining. Individual participant data showing volumes of intracellular (red) and extracellular (blue) compartments at baseline and then after one and three months of detraining.

Table 1: Clinical characteristics subjects presented as mean \pm standard deviation or median (interquartile range)

	Baseline	One month detraining	P value vs baseline	Three months detraining	P value vs baseline	P value vs 1 month
N	28	28		23		
Age	24 (21 - 30)					
Male Sex (%)	23 (82)	23 (82)		20 (87)		
Height (cm)	177 \pm 8					
Weight (kg)	78 \pm 14	77 \pm 12	0.21	76 \pm 12	1.0	1.0
Hours per week spent training	7 (5 - 9)	0 (0 - 0)	<0.0001	0.5 (0 - 6)	<0.0001	0.0001
Heart Rate	65 \pm 10	68 \pm 11	0.20	62 \pm 9	0.19	0.05
Systolic Blood Pressure (mmHg)	121 (118 - 131)	122 (114 - 130)	0.39	119 (113 - 124)	0.01	0.17
Diastolic Blood Pressure (mmHg)	64 (60 - 75)	65 (57 - 72)	0.64	63 (54 - 68)	0.16	0.18

Table 2: Electrocardiogram findings

	Baseline	One month detraining	P value vs baseline	Three months detraining	P value vs baseline	P value vs 1 month
Heart Rate (bpm)	67 ± 11	70 ± 9	0.17	64 ± 8	0.06	0.05
PR interval (s)	145 ± 21	148 ± 22	0.13	147 ± 19	0.64	1.0
QTc interval (s)	410 ± 19	416 ± 22	0.08	409 ± 21	1.0	0.45
SV ₂ , mV	14 ± 6	14 ± 6	0.36	14 ± 5	0.52	1.0
RV ₅ , mV	16 ± 5	14 ± 4	0.006	16 ± 6	1.0	1.0
Sokolow-Lyon Product, mV	31 ± 8	29 ± 8	0.01	30 ± 7	0.82	0.52
Incomplete RBBB, n (%)	5 (18)	4 (14)		4 (17)		
T wave inversion, n (%)	1 (4)	1 (4)		0 (0)		

Table 3: Cardiovascular magnetic resonance findings

	Baseline	One month detraining	P value vs baseline	Three months detraining	P value vs baseline	P value vs 1 month
LV EDV (ml)	190 ± 32	182 ± 30	0.003	188 ± 35	1.0	0.38
LV EDV index (ml/m ²)	98 ± 13	94 ± 15	0.007	98 ± 17	1.0	0.34
LV ESV (ml)	76 ± 17	75 ± 17	0.72	81 ± 21	0.18	0.37
LV EF (%)	60 ± 5	59 ± 5	0.27	57 ± 5	0.07	0.69
LV mass (g)	130 ± 28	121 ± 25	<0.0001	121 ± 23	0.0007	1.0
LV mass index (g/m ²)	66 ± 10	62 ± 11	0.0005	63 ± 11	0.02	1.0
RV EDV (ml)	188 ± 39	181 ± 35	0.03	180 ± 35	0.59	1.0
RV EDV index (ml/m ²)	97 ± 17	93 ± 15	0.02	93 ± 13	0.53	1.0
RV ESV (ml)	80 ± 18	81 ± 15	0.76	81 ± 19	1.0	1.0
RV EF (%)	57 ± 6	55 ± 5	0.02	55 ± 7	0.51	1.0
Native T1 (ms)	1225 ± 30	1239 ± 30	0.02	1228 ± 47	1.0	0.79
ECV (%)	24.5 ± 2.3	26.0 ± 2.6	0.0007	25.6 ± 2.8	0.04	1.0
Extracellular compartment volume (ml)	30 ± 5	30 ± 5	0.49	29 ± 5	1.0	1.0
Intracellular Compartment volume (ml)	94 ± 22	85 ± 19	<0.0001	86 ± 18	0.0002	1.0
Circumferential strain Apex (%)	12.8 ± 4.5	13.2 ± 3.1	0.61	14.0 ± 3.2	0.57	0.32
Circumferential strain Mid LV (%)	13.4 ± 4.5	14.5 ± 2.7	0.30	14.1 ± 2.3	1.0	1.0
Circumferential strain Base (%)	13.0 ± 4.1	14.4 ± 2.6	0.06	14.1 ± 2.9	0.45	1.0